CLAIMS

We claim:

1. A method of treating cancer in a mammal, comprising: administering to said mammal

(a) a compound of formula I

$$\begin{array}{c|c} D & X_4 \\ W & N \\ N & H \\ Q_1 \\ \end{array}$$

or a salt, solvate, or physiologically functional derivative thereof; wherein:

D is

$$X_1$$
 X_2
 X_3
 X_2
 X_3
 X_4
 X_4
 X_5
 X_5

 X_1 is hydrogen, $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, or C_{1-4} hydroxyalkyl;

 X_2 is hydrogen, $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, $C(O)R^1$, or aralkyl;

X₃ is hydrogen or halogen;

 X_4 is hydrogen, C_{1^-4} alkyl, C_{1^-4} haloalkyl, heteroaralkyl, cyanoalkyl, -(CH₂)_pC=CH(CH₂)_tH, -(CH₂)_pC=C(CH₂)_tH, or C₃₋₇ cycloalkyl;

p is 1, 2, or 3;

t is 0 or 1;

W is N or C-R, wherein R is hydrogen, halogen, or cyano;

 Q_1 is hydrogen, halogen, $C_{1^{-2}}$ haloalkyl, $C_{1^{-2}}$ alkyl, $C_{1^{-2}}$ alkoxy, or $C_{1^{-2}}$ haloalkoxy;

 Q_2 is A^1 or A^2 ;

 Q_3 is A^1 when Q_2 is A^2 and Q_3 is A^2 when Q_2 is A^1 ;

wherein

 A^1 is hydrogen, halogen, C_{1^-3} alkyl, C_{1^-3} haloalkyl, -OR¹, and A^2 is the group defined by -(Z)_m-(Z¹)-(Z²), wherein

Z is CH_2 and m is 0, 1, 2, or 3, or

Z is NR² and m is 0 or 1, or

Z is oxygen and m is 0 or 1, or

Z is CH₂NR² and m is 0 or 1;

 Z^1 is $S(O)_2$, S(O), or C(O); and

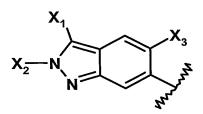
 Z^2 is C_{1} - C_4 alkyl, NR^3R^4 , aryl, arylamino, aralkyl, aralkoxy, or heteroaryl;

R¹ is C₁₋₄ alkyl;

 R^2 , R^3 , and R^4 are each independently selected from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, $-S(O)_2R^5$, and $-C(O)R^5$;

R⁵ is C₁₋₄ alkyl, or C₃₋₇ cycloalkyl; and

when Z is oxygen then Z^1 is $S(O)_2$ and when D is



then X_2 is $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, $C(O)R^1$, or aralkyl; and (b) a compound of formula II

or a salt, solvate, or physiologically functional derivative thereof; wherein

Y is CR⁶ and V is N; or Y is CR⁶ and V is CR⁷;

 R^6 represents a group $CH_3SO_2CH_2CH_2NHCH_2$ -Ar-, wherein Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

 R^7 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkylamino and di[C_{1-4} alkyl]amino;

U represents a phenyl, pyridyl, $3\underline{H}$ -imidazolyl, indolyl, isoindolyl, indolyl, isoindolyl, $1\underline{H}$ -indazolyl, 2,3-dihydro- $1\underline{H}$ -indazolyl, $1\underline{H}$ -benzimidazolyl, 2,3-dihydro- $1\underline{H}$ -benzimidazolyl or $1\underline{H}$ -benzotriazolyl group, substituted by an R^8 group and optionally substituted by at least one independently selected R^9 group;

R⁸ is selected from the group consisting of benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl; or R⁸ represents trihalomethylbenzyl or trihalomethylbenzyloxy; or R⁸ represents a group of formula

wherein each R^{10} is independently selected from halogen, $C_{1\text{--}4}$ alkyl and $C_{1\text{--}4}$ alkoxy; and n is 0 to 3; and

each R^9 is independently hydroxy, halogen, $C_{1\text{-}4}$ alkyl, $C_{2\text{-}4}$ alkenyl, $C_{2\text{-}4}$ alkynyl, $C_{1\text{-}4}$ alkoxy, amino, $C_{1\text{-}4}$ alkylamino, di[$C_{1\text{-}4}$ alkyl]amino, $C_{1\text{-}4}$ alkylthio, $C_{1\text{-}4}$ alkylsulphinyl, $C_{1\text{-}4}$ alkylsulphonyl, $C_{1\text{-}4}$ alkylcarbonyl, carboxy, carbamoyl, $C_{1\text{-}4}$ alkoxycarbonyl, $C_{1\text{-}4}$ alkanoylamino, N-($C_{1\text{-}4}$ alkyl)carbamoyl, N,N-di($C_{1\text{-}4}$ alkyl) carbamoyl, cyano, nitro and trifluoromethyl.

 The method of claim 1, wherein (a) the compound of formula I is a compound of formula I^a

or a salt, solvate or physiologically functional derivative thereof; wherein Q_3 is A^1 when Q_2 is A^2 and Q_3 is A^2 when Q_2 is A^1 ; wherein

 A^1 is hydrogen, halogen, C_{1^-3} alkyl, and A^2 is the group defined by $-(Z)_m$ - (Z^1) - (Z^2) , wherein Z is CH_2 and m is 0, 1, 2, or 3; Z^1 is $S(O)_2$, S(0), or C(O); and Z^2 is C_{1^-4} alkyl, or NR^3R^4 ;

 \mbox{R}^3 and \mbox{R}^4 are each independently selected from hydrogen, or $\mbox{C}_{1\mbox{-}4}$ alkyl; and

(b) the compound of formula II is a compound of formula IIa

or a salt, solvate or physiologically functional derivative thereof; wherein R¹¹ is –Cl or –Br, X is CH , N, or CF, and Z is thiazole or furan.

3. The method of claim 1, wherein (a) the compound of formula I is a compound of formula $I^{\rm b}$

or a salt, solvate, or physiological functional derivative thereof; and (b) the compound of formula II is a compound of formula II^b

or a salt, solvate, or physiological functional derivative thereof.

4. The method of claim 1, wherein (a) the compound of formula I is a monohydrochloride salt of a compound of formula I ^b

; and

(b) the compound of formula II is a monohydrate ditosylate salt of a compound of formula II $^{\rm b}$

5. The method of claim 1, wherein the compound of formula I is a monohydrochloride salt of a compound of formula I ^b

$$H_3C$$
 N
 CH_3
 CH_3
 NH_2
 $NH_$

; and

WO 2005/105094

(b) the compound of formula II is an anhydrous ditosylate salt of a compound of formula II $^{\mbox{\scriptsize b}}$

$$\begin{array}{c|c} H_3C, 0 \\ & & \\$$

6. A pharmaceutical composition comprising:

(a) a compound of formula I

$$\begin{array}{c|c}
D & X_4 & Q_3 \\
W & N & H & Q_3 \\
N & N & H & Q_1
\end{array}$$
(I)

or a salt, solvate, or physiologically functional derivative thereof;

65

wherein:

D is

$$X_1$$
 X_2
 X_3
 X_2
 X_3
 X_4
 X_4
 X_5
 X_5

 X_1 is hydrogen, $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, or C_{1-4} hydroxyalkyl;

 X_2 is hydrogen, $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, $C(O)R^1$, or aralkyl;

X₃ is hydrogen or halogen;

X₄ is hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, heteroaralkyl, cyanoalkyl,

 $\hbox{-(CH$_2)$_p$C=CH(CH$_2)$_t$H, -(CH$_2)$_p$C\equivC(CH$_2)$_t$H, or C_{3-7} cycloalkyl;}$

p is 1, 2, or 3;

t is 0 or 1;

W is N or C-R, wherein R is hydrogen, halogen, or cyano;

 Q_1 is hydrogen, halogen, $C_{1^{-2}}$ haloalkyl, $C_{1^{-2}}$ alkyl, $C_{1^{-2}}$ alkoxy, or $C_{1^{-2}}$ haloalkoxy;

 Q_2 is A^1 or A^2 ;

 Q_3 is A^1 when Q_2 is A^2 and Q_3 is A^2 when Q_2 is A^1 ;

wherein

 A^1 is hydrogen, halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, -OR¹, and

 A^2 is the group defined by $-(Z)_m-(Z^1)-(Z^2)$, wherein

Z is CH_2 and m is 0, 1, 2, or 3, or

Z is NR² and m is 0 or 1, or

Z is oxygen and m is 0 or 1, or

WO 2005/105094

PCT/US2005/012337

66

Z is CH_2NR^2 and m is 0 or 1; Z^1 is $S(O)_2$, S(O), or C(O); and Z^2 is C_{1-4} alkyl, NR^3R^4 , aryl, arylamino, aralkyl, aralkoxy, or heteroaryl;

R¹ is C₁₋₄ alkyl;

 R^2 , R^3 , and R^4 are each independently selected from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, $-S(O)_2R^5$, and $-C(O)R^5$;

 R^5 is $C_{1\text{--}4}$ alkyl, or $C_{3\text{--}7}$ cycloalkyl; and

when Z is oxygen then Z¹ is S(O)₂ and when D is

$$X_2$$
 X_2
 X_3
 X_2
 X_3

then X_2 is $C_{1^{-4}}$ alkyl, $C_{1^{-4}}$ haloalkyl, $C(O)R^1$, or aralkyl; and (b) a compound of formula II

or a salt, solvate, or physiologically functional derivative thereof; wherein

Y is CR⁶ and V is N;

or Y is CR⁶ and V is CR⁷;

 R^6 represents a group $CH_3SO_2CH_2CH_2NHCH_2$ -Ar-, wherein Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups; R^7 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkylamino and di[C_{1-4} alkyl]amino;

U represents a phenyl, pyridyl, 3 \underline{H} -imidazolyl, indolyl, isoindolyl, indolyl, isoindolyl, 1 \underline{H} -indazolyl, 2,3-dihydro-1 \underline{H} -indazolyl, 1 \underline{H} -benzimidazolyl, 2,3-dihydro-1 \underline{H} -benzimidazolyl or 1 \underline{H} -benzotriazolyl group, substituted by an R^8

group and optionally substituted by at least one independently selected R⁹ group;

R⁸ is selected from the group consisting of benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl; or R⁸ represents trihalomethylbenzyl or trihalomethylbenzyloxy; or R⁸ represents a group of formula

wherein each R^{10} is independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy; and n is 0 to 3; and each R^9 is independently hydroxy, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylsulphonyl, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoylamino, C_{1-4} alkyl)carbamoyl, C_{1-4} alkyl)carbamoyl, cyano, nitro and trifluoromethyl.

7. The pharmaceutical composition of claim 6, wherein (a) the compound of formula I is a compound of formula I^a

or a salt, solvate or physiologically functional derivative thereof; wherein Q_3 is A^1 when Q_2 is A^2 and Q_3 is A^2 when Q_2 is A^1 ; wherein

A¹ is hydrogen, halogen, C₁₋₃ alkyl, and

 A^2 is the group defined by $-(Z)_m$ - (Z^1) - (Z^2) , wherein Z is CH_2 and m is 0, 1, 2, or 3; Z^1 is $S(O)_2$, S(0), or C(O); and Z^2 is C_{1^2} alkyl, or NR^3R^4 ;

 R^3 and R^4 are each independently selected from hydrogen, or $C_{1^{-4}}$ alkyl; and

(b) the compound of formula II is a compound of formula II a

or a salt, solvate or physiologically functional derivative thereof; wherein R^{11} is -CI or -Br, X is CH, N, or CF, and Z is thiazole or furan.

8. The pharmaceutical composition of claim 6, wherein (a) the compound of formula I is a compound of formula I b

or a salt, solvate, or physiological functional derivative thereof; and (b) the compound of formula II is a compound of formula II b

or a salt, solvate, or physiological functional derivative thereof.

9. The pharmaceutical compostion of claim 6, wherein (a) the compound of formula I is a monohydrochloride salt of a compound of formula I b

; and

(b) the compound of formula II is a monohydrate ditosylate salt of the compound of formula II $^{\rm b}$

10. The pharmaceutical composition of claim 6, wherein (a) the compound of formula I is a monohydrochloride salt of a compound of formula I ^b

; and

(b) the compound of formula II is an anhydrous ditosylate salt of the compound of formula II $^{\rm b}$

- 11. A pharmaceutical combination comprising: a compound of formula I, I^a or I^b or salt, solvate or physiologically functional derivative thereof, and a compound of formula II, II^a or II^b or salt, solvate or physiologically functional derivative thereof for use in therapy.
- 12. The use of a pharmaceutical combination comprising: a compound of formula I, I^a or I^b or salt, solvate or physiologically functional derivative thereof, and a compound of formula II, II^a or II^b or salt, solvate or physiologically functional derivative thereof for the preparation of a medicament useful in the treatment of cancer.